REMARKS

Status of the Claims

Claims 1-13, 20-22, and 24-34 are pending in the current application. Claims 27-34 have been withdrawn from consideration. Claims 14-19, and 23 have been cancelled without prejudice to or disclaimer of the subject matter contained therein. Claims 1-3, 8, 9, 20-22, and 24 have been amended as described elsewhere herein. No new matter has been added by amendment. Reexamination and reconsideration are respectfully requested.

The Restriction Requirement

Applicants affirm the election with traverse of Group I, claims 1-26.

The Objections to the Specification Should be Withdrawn

The specification has been objected to on the grounds that it contains embedded hyperlinks. The specification has been amended to delete the hyperlinks on pages 12 and 18 as suggested by the Examiner. The web site reference for the *Lemna gibba* codon usage table for GenBank Release 113.0 has been replaced by a reference to new Table 5, which contains the codon usage table for this GenBank release. A copy of the print out of this table made before July 31, 2000, the filing date of the earliest priority document for the present application, is attached as Appendix A. Accordingly, it is respectfully requested that the objection to the specification be withdrawn.

The Rejection Under 35 U.S.C.§ 112, Second Paragraph, Should be Withdrawn

Claims 1-26 have been rejected under 35 U.S.C. § 112, second paragraph on the grounds that they are indefinite. The rejection is respectfully traversed for the reasons described below.

Claim 1(b) has been rejected under 35 U.S.C. § 112 on the grounds that the phrase "biologically active polypeptide" lacks antecedent basis. This rejection is rendered moot by amendments to this claim.

Claim 2 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that they are incomplete because the desired product is not produced in the final step of the method. Applicants respectfully traverse the rejection. The preamble of claim 1 recites a method of producing a biologically active α-2b-interferon, and the final step of the claim recites the step of collecting the biologically active α-2b-interferon from the duckweed culture medium. Accordingly, one of skill in the art, when reading claim 1 in light of the supporting specification would be able to ascertain with a reasonable degree of precision the particular area circumscribed by this claim.

Claim 2 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that it should properly be included as a step in the method of claim 1. The rejection is respectfully traversed. Secretion of the biologically active α-2b-interferon into the duckweed media is not required in the method of claim 1, because the biologically active α-2b-interferon may also be collected directly from the tissue. See, for example, Example 1 on pages 30-31 and Figures 1 and 2. Accordingly, one of skill in the art would be able to ascertain the scope of the claim.

Claims 3 and 9(b) have been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that it is unclear what the plant-preferred translation initiation context nucleotide sequence is or where it would be place with reference to the other components. A description of the plant-preferred translation initiation context nucleotide sequence and its placement is provided on lines 8-11 of page 7 of the specification. Accordingly, one of skill in the art, when reading claims 3 and 9 in light of the supporting specification would be able to ascertain with a reasonable degree of precision the particular area circumscribed by this claim.

Claim 14 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that there is no antecedent basis for the phrase "duckweed frond culture." Claim 14 has been cancelled, thereby rendering the rejection of this claim moot.

Claim 17 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the term "therapeutic" is indefinite. Claim 17 has been cancelled, thereby rendering the rejection of this claim moot.

Claim 18 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the term "biological activity" is indefinite. Claim 17 has been cancelled, thereby rendering the rejection of this claim moot.

Claim 19 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the term "α-2b-interferon" is indefinite because it needs an article in front of it. Claim 19 has been cancelled, thereby rendering the rejection of this claim moot.

Claim 20 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the term "human α-2b-interferon" is indefinite because it needs an article in front of it. Claim 20 has been amended as suggested by the Examiner, thereby overcoming the rejection.

Claim 24 has been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that there is no antecedent basis for the phrase "signal peptide sequence." Claim 24 has been amended to delete the term "sequence," thereby overcoming the rejection.

In view of the above amendments and remarks, all grounds of rejection under 35 U.S.C. § 112, second paragraph, have been overcome. Reconsideration and withdrawal of the rejection are respectfully requested.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Claims 3-7, 9-13 and 22 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that they recite subject matter which was not described in the specification in such a way as the reasonably convey to one skilled in the relevant art that the inventors had possession of the application at the time the invention was filed. The rejection is respectfully traversed for the reasons described below.

The Examiner argues that insufficient written description is provided for the duckweed-preferred codons recited in claims 3-7 and 9-13 because the specification defines these codons as those having a frequency of greater than 17%, but does not describe which codons these are. Applicants note that methods for determining the preferred codon usage for a particular species were well know in the art at the time the instant application was filed, and are additionally described on lines 1-25 of page 18 the specification and the references cited therein. As noted on lines 5-7 of page 18, the duckweed-preferred codons may be determined from the codons of highest frequency in the proteins expressed in duckweed. Duckweed proteins and their coding sequences are readily available to those of skill in the art in sequence databases including GenBank. Accordingly, the application conveys to one of skill in the art that the inventors were in possession of the duckweed-preferred codons at the time the instant application was filed.

Claim 22 was rejected under 35 U.S.C. § 112, first paragraph, on the grounds that no structural element is recited for the claimed biologically active variants having 80% sequence identity with the amino acid sequence set forth in SEQ ID NO:4 or the amino acid sequence set forth in SEQ ID NO:5. The rejection is respectfully traversed for the reasons described below.

The "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, 'Written Description' Requirement" (66 Fed. Reg. 1099 (2001)), state that the written description requirement may be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant, identifying characteristics . . . i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." 66

Fed. Reg. at 1106. This requirement is in accordance with *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997), where the court held that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, or chemical name' of the claimed subject matter sufficient to distinguish it from other materials." 119 F.3d at 1568, citing *Fiers v. Revel* 984 F.2d 1164 (Fed. Cir. 1993).

The written description provided for the polypeptides in claim 22 meets this requirement, because the claim recites the identifying structural characteristics that define the claimed genus of α-2b-interferon variants. This claim recites that the α-2b-interferon variants have at least 80% sequence identity with an amino acid sequence selected from the group consisting of the amino acid sequence set forth in SEQ ID NO:4 and the amino acid sequence set forth in SEQ ID NO:4 . This structural limitation is sufficient to distinguish the claimed polypeptides from other materials and thus sufficiently defines the claimed genus of α-2b-interferon variants.

Applicants have further provided the functional characteristics that distinguish the claimed sequences of the genus. Specifically, the claim recites *biologically active* α-2b-interferon Accordingly, both the structural properties and the functional properties that characterize the claimed genus of polypeptides are specifically recited in the claims. Furthermore, the specification discloses a number of α-2b-interfereon variants falling within with structural and functional limitations of the claims. *See*, lines 6-8 of page 23.

The subject matter of claim 22 is analogous to Example 14 of the "Revised Interim Written Description Guidelines Training Materials" available at www.uspto.gov/web/menu/written.pdf. Example 14 is directed to a generic claim: a protein having at least 95% sequence identity to the sequence of SEQ ID NO:3, wherein the sequence catalyzes the reaction A → B. The analysis of Example 14 in the Training Materials does not conclude that the genus of sequences is insufficiently described because the specification does not demonstrate the structural motifs underlying the function of the claimed polypeptide. Rather, the conclusion in the Training Materials is that the generic claim of Example 14 is sufficiently described under § 112, first paragraph, because 1) "the single sequence disclosed in SEQ ID

NO:3 is representative of the genus" and 2) the claim recites a limitation requiring the compound to catalyze the reaction from A → B, and therefore one of skill in art would recognize that the Applicants were in possession of the necessary common attributes possessed by the members of the genus.

Thus, claim 22 provides the relevant, identifying characteristics that describe the claimed genus of sequences as required by the applicable case law, and one of skill in the art would recognize that the inventors were in possession of the claimed invention. Therefore, the requirement for a written description of the claimed invention under 35 U.S.C. § 112, first paragraph, is met.

Claims 3-7 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that they do not enable one of skill in the art to make and use the claimed invention. The rejection is respectfully traversed for the reasons described below.

The Examiner argues that present invention does not enable the use of the duckweed-preferred codons recited in claims 3-7 because the specification defines these codons as those having a frequency of greater than 17%, but does not describe which codons these are. As noted above in response to the rejection for insufficient written description, methods for determining the preferred codon usage for a particular species were well know in the art at the time the instant application was filed, and are additionally described on lines 1-25 of page 18 the specification and the references cited therein. As noted on lines 5-7 of page 18, the duckweed-preferred codons may be determined from the codons of highest frequency in the proteins expressed in duckweed. Duckweed proteins and their coding sequences are readily available to those of skill in the art in sequence databases including GenBank. Accordingly, the specification provides sufficient guidance to allow one of skill in the art to make and use the claimed invention.

The Examiner argues that the Applicants citation of a website for the Codon Usage Database does not provide enablement for the claimed invention because the content of the website may change at any time. Applicants note that a particular Release number for the database *i.e.* GenBank Release 113.0, has been cited and thus the cited content is fixed. *See*, line

22 on page 12 of the specification. The specification has been amended to insert the codon usage for *Lemna gibba* from GenBank Release 113.0 as Table 5. A copy of the codon usage table for Release 113.0 is attached as Appendix A. This table was printed prior to July 31, 2000, the filing date of the earliest priority document for the present application.

Claims 8-13 have been rejected under 35 U.S.C. § 112, first paragraph on the grounds that it is not clear which of expression constructs listed in Table 1 have a translation initiation codon that is flanked by a plant-preferred translation initiation context nucleotide sequence and which constructs comprise a plant intron. The rejection is respectfully traversed.

The specification provides sufficient guidance to allow one of skill in the art to make and use the nucleotides sequences recited in claims 8-13. Lines 23-27 on page 25 of the specification teach that the pBMSP-3 vector contains an intron from the maize alcohol dehydrogenase gene, and Table 1 shows which vector was used for each expression. The constructs containing the maize alcohol dehydrogenase intron are also described on lines 2-4 of page 34 of the specification. Additional examples of plant introns that may be used to enhance expression are described on line 28 of page 19 through line 6 of page 20. All of the expression constructs listed in Table 1 contain a plant-preferred translation initiation context nucleotide sequence, with the exception of IFN01. In addition, plant-preferred translation initiation context nucleotide sequences are described on lines 4-14 of page 19 of the specification. Accordingly, the level of experimentation required to make and use the nucleotide sequences recited in claims 8-13 would not be undue.

The Examiner argues that the specification does not allow one of skill in the art to make and use human α-2b-interferon coding sequences and other sequences cited in Table 1 because the support for these sequences is provided in the form of GenBank Accession numbers rather than as a SEQ ID NO. Applicants do not agree that the material incorporated by reference is essential material because the sequences incorporated by reference are merely examples of sequences that may be used in the claimed methods and are not required to describe the claimed

invention, provide an enabling disclosure of the claimed invention, or describe the best mode for the invention. Nevertheless, in order to expedite prosecution, the interferon sequence listed in Table 1, the sequence of the maize alcohol dehydrogenase intron described on lines 24-26 of page 25 and the interferon and *Arabidopsis thaliana* endochitinase signal peptide sequences listed in Table 1 have been added to the sequence listing, and the specification has been amended to recite the appropriate sequence identifiers. The sequences added to the sequence listing consist of the same material incorporated by reference in the instant application. No new matter is added by way of this amendment.

Claim 22 has been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide sufficient enablement to allow one of skill in the art to make and use biologically active α-2b-interferon variants having at least 80% sequence identity with the amino acid sequence set forth in SEQ ID NO:4 or the amino acid sequence set forth in SEQ ID NO:5. The rejection is respectfully traversed for the reasons described below.

According to the applicable case law, an enabling disclosure must describe the claimed invention in such a way as to enable the ordinarily skilled artisan to make and use the invention, and this description be commensurate with the scope of the claimed invention. The test of enablement is not whether experimentation is necessary, but rather if experimentation *is* necessary, whether it is undue. *In re Angstadt*, 198 USPQ 214, 219 (C.C.P.A. 1976). The test of whether an invention requires undue experimentation is not based on a single factor, but rather a conclusion reached by weighing many factors. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Factors to be considered in determining whether undue experimentation is required include the quantity of experimentation necessary, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the breadth of the claimed invention. 8 USPQ2d at 1404. Accordingly, the holding of *Wands* does not require that an applicant identify every variant meeting the structural and

functional limitation of the claim. Rather, *Wands* sets out factors to be considered in determining whether undue experimentation is required to make and use the claimed functional variants.

In the present case, Applicants have provided sufficient guidance to allow one of skill in the art to make and use α-2b-interferon variants that meet the structural and functional limitations of the claims. The specification discloses a number of working examples of such variants on lines 7-8 on page 23, and provides assays for interferon activity on pages 29-30. Based on the number of working examples of α-2b-interferon provided in the specification, a skilled artisan could choose among possible modifications to produce polypeptides within the structural parameters set forth in the claims and test these modified variants to determine if they retain the interferon activity of the polypeptides given in SEQ ID NO:4 or SEQ ID NO:5. Making and testing such variants is routine to those of skill in the art. Furthermore, the scope of the claims is limited to variants that fall within the defined structural parameters and are biologically active.

Accordingly, when all of the *Wands* factors are considered together, it is clear that although some quantity of experimentation would be required to produce functional α-2b-interferon variants, the level of experimentation would not be undue in view of the state of the prior art (where residues required for interferon activity have been described), the relative skill of those in the art (to whom the making and testing of variants is routine), the predictability in the art, the amount of direction provided in the specification (which provides guidance regarding assays for identifying functional interferon variants), the breadth of the claimed invention (for which the scope is defined by both structural and functional limitations), and the existence of working examples of interferon variants. These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 112, first paragraph, have been overcome. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

The Rejection Under 35 U.S.C. § 102 Should be Withdrawn

Claims 1, 2, 8, 15, 16, 17, 18, and 23 have been rejected under 35 U.S.C. § 102(b) on the grounds that they are anticipated by PCT Publication WO 99/07210. The rejection is respectfully traversed as applied to the amended claims.

WO 99/070210 teaches a method of producing a biologically active recombinant polypeptide in a duckweed culture, where the coding sequence for the polypeptide is operably linked to a coding sequence for a signal peptide that directs the secretion of the polypeptide into the culture medium. This publication teaches the use of nucleotide sequences that have been modified for enhanced expression in duckweed, and further teaches the expression of a number of polypeptides, including mammalian alpha interferon.

Claims 1 and 8 have been amended to recite a method for producing biologically active α-2b-interferon in a duckweed plant culture or duckweed nodule culture. WO 99/070210 does not teach the production of α-2b-interferon; accordingly, this reference does not teach every element of claims 1 and 8 as amended.

In view of the above amendments, the rejection under 35 U.S.C. § 102(b) has been overcome. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSIONS

It is believed that all the rejections have been obviated or overcome and the claims are in conditions for allowance. Early notice to this effect is solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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In re: Stomp et al.
Appl. No. 09/915,873
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APPENDIX A